A-20482.CON PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

Allen PATTERSON *et al.*

Serial No: 09/159,680 Group Art Unit: 1614

Filed: September 24, 1998 Examiner: J. Goldberg

For: LONG-ACTING OXYTETRACYCLINE COMPOSITION

DECLARATION OF SEAN DUFFY UNDER 37 C.F.R. §1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

The undersigned, Sean Duffy, declares that:

he is Project Manager of Research and Development for Norbrook Laboratories Limited, a company having rights in the above-identified patent application;

he is a citizen of Ireland residing at 57 Tullinavall Road, Cullyhanna, Newry, Co. Down;

he has reviewed the above-identified U.S. patent application and understands the invention claimed therein;

he is familiar with the art to which the claimed invention is directed, having received the Degree of Bachelor of Science in Biochemistry (School of

Biochemistry, The Queen's University of Belfast), Year of Degree: 1988 and Degree of Doctor of Philosophy (School of Medicine, The Queen's University of Belfast), Year of Degree: 1991, and having been employed in that art for 8 years;

in connection with his studies and work in that art, he has developed an understanding as to the level of skill of one having ordinary skill in the art at the time the invention in the above-identified application was made;

he has reviewed and understands the references of record in the present application, namely, Malook *et al* (U.S. Patent No. 4,772,460), Zupan *et al* (U.S. Patent No. 5,075,295) and the European reference (European Patent Application No. 0,038,013);

he made two formulations, Formulation (1) and Formulation (2), which attempted to combine the compositions disclosed in Zupan *et al* with those disclosed in the European reference;

Formulation (1) contained 40% by weight polyethylene glycol 400 from Zupan *et al* and was made to volume with glycerol formal from the European reference;

Formulation (2) contained 20% by weight polyethylene glycol 400 from Zupan *et al* and was made to volume with glycerol formal from the European reference;

Formulation (1) was:

Oxytetracycline Dihydrate	30% w/v
Magnesium Oxide	2.7% w/w
Sodium formaldehyde sulfoxylate	0.4% w/w
Polyethylene Glycol 400 (PEG 400)	40% w/w
Distilled water	10%
Monoethanolamine	q.s.
Glycerol Formal (GF)	ad 100%;

Formulation (2) was:

Oxytetracycline Dihydrate	30% w/v
Magnesium Oxide	2.7% w/w
Sodium formaldehyde sulfoxylate	0.4% w/w
Polyethylene Glycol 400 (PEG 400)	20% w/w
Distilled water	10%
Monoethanolamine	q.s.
Glycerol Formal (GF)	ad 100%;

in the aqueous solution in both formulations, water was kept to 10%, which is minimal for an aqueous solution;

the maximum percentage by weight of glycerol formal which could be added in Formulation (1) and (2) was 28% and 41%, respectively;

both formulations were quite dark in colour and exhibited great difficulty in filtration in that the filtration time would have been in the region of

three to four times longer when compared to the filtration time for the composition of the present invention;

the syringeability of both formulations through an 18-gauge needle was completely unsatisfactory as neither Formulation (1) or (2) passed easily through an 18-gauge needle as per the conventional test for syringeability.

Due to these physical characteristics, neither formulation would be a viable commercial product, and would not have been taken to animal field trial stage.

In addition, Formulations (1) and (2) were re-analysed for syringeability and viscosity after 5 months storage at room temperature and the results were compared to two samples of the composition of the present invention: Sample (A) was manufactured in 1996 and Sample (B) was freshly prepared. On initial inspection a sediment had formed in both Formulation (1) and (2) which required vigorous shaking to disperse. Such a sediment was not present in either Sample (A) or (B). Formulation (1) and (2) did not comply with the test for syringeability as neither formulation passed easily through an 18-gauge needle but Samples (A) and (B) complied with this test. To further quantify the parameter of syringeability, each formulation was tested for the time taken to fill 5 ml from a 100 ml vial using an 18-gauge needle and a 10 ml syringe. The result obtained are as follows:

	Time (secs)
Formulation (1)	60
Formulation (2)	35
Sample (A)	6
Sample (B)	10

The viscosity of each formulation was then measured at 10 rpm at room temperature and the results are as follows:

	Viscosity (cps)
Formulation (1)	668
Formulation (2)	384
Sample (A)	80
Sample (B)	124

From these results, it is evident that the physical characteristics of Formulation (1) and (2) deemed them totally unacceptable as commercial product formulations. Initially, at manufacture, physical assessment demonstrated that these formulations would have no commercial potential and re-analysis of these parameters after five months storage at room temperature re-enforces this view. This is especially evident when the five month old formulations are compared to the composition of the invention which was manufactured in 1996.

Polyethylene glycol 200 is a polymeric glycol with a molecular weight of approximately 200;

polyethylene glycol 200 is different from PEG 400 in physical and chemical properties and in its uses in various disciplines;

polyethylene glycol 200 has a mean molecular weight range of 190 to 210 while polyethylene glycol 400 has a mean molecular weight range of 380 to 420. Thus the increase in molecular weight is manifested as an increase in viscosity of a solution of PEG 400 in comparison to a solution of PEG 200 of the same concentration. The increase in viscosity renders PEG 400 completely unsuitable for use in the composition of this invention in terms of manufacture (elongated filter times), syringeability of the parenteral product and the potential of irritancy to the target animal.

In addition to the composition according to the present invention, Norbrook Laboratories Limited considered using Dimethylacetamide, N-methyl pyrrolidone (NMP) formulations.

Pharmacokinetic study data in cattle for those formulations that were considered to have commercial potential are given below along with corresponding data for a composition according to the present invention, Product No. 040:

the composition according to the present invention also exhibited a greater maximum concentration in bovine plasma (cmax) and provided for a greater overall distribution over time (AUC).

In order to determine the optimum concentration of each solvent in a composition it is necessary to perform pharmacokinetic studies in the target animal;

the results below demonstrate how subtle changes in a solvent system resulted in significant changes in the pharmacokinetic profile of porcine plasma;

	Product No: AL-060	Product No: AL-040
C max	3.067	3.163
AUC	71.549	73.068

Product No: AL-060 comprised the composition of the present invention with the following solvent system: 30% Glycerol Formal and 20% Polyethylene Glycol 200, whereas Product No: AL-040 comprised the same quantitative components with a solvent system consisting of 40% Glycerol Formal and 10% Polyethylene Glycol 200.

From the results obtained, it is evident that AL-040 has a greater Cmax and greater AUC than AL-060 indicating that AL-040 attains a greater maximum concentration in the plasma and a greater overall distribution over time.

	Product No.: 010 NMP 60% (30% oxytet)	Product No.: 020 NMP 30% (30% oxytet)	Product No.: 040 GF 40% PEG10% (20% oxytet)
cmax	9.4	9.95	11.94
AUC	266.5	293.0	328.3

in which "GF" stands for glycerol formal, "PEG" stands for polyethylene glycol 200, "oxytet" stands for oxytetracycline, "cmax" stands for maximum concentration of oxytetracycline in bovine plasma, and "AUC" stands for area under the curve, which is a measure of the distribution of the concentration in the bovine plasma over time.

The N-methyl pyrrolidone formulations comprise as follows:

	Product No: 010	Product No: 020
Oxytetracycline (% w/v)	30	30
Magnesium oxide (% w/v)	2.7	2.7
SFS (% w/v)	0.4	0.4
N-methyl pyrrolidone	60	30
Water (%)	ad 100%	ad 100%

It can be seen that the composition according to the present invention, which contained 20% oxytetracycline, exhibited a better pharmacokinetic profile than the NMP formulations with 30% oxytetracycline;

It is therefore evident, from the presented bovine and porcine pharmacokinetic data, that both the type of solvent used, and its concentration, in a given formulation can directly affect the pharmacokinetic profiles for that formulation.

The plasma study data in the European reference demonstrate that effective levels of the antibiotic in plasma were attained for up to about four days;

compositions according to the present invention containing a tetracycline compound in a water miscible solvent system comprising glycerol formal in an amount of from about 10 to about 50% v/v and polyethylene glycol in an amount of from about 1 to 15% v/v provided effective levels of the tetracycline compound in bovine plasma for more than nine days;

previously known products have provided effective levels of the tetracycline compound in plasma for only up to about four days;

based on his knowledge of solvents, he would not expect the interchanging of solvents in general or the addition of polyethylene glycol in an amount disclosed in Zupan *et al* to glycerol formal in an amount disclosed in the European reference to have any foreseeable benefit whatsoever.

He further declares that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful false statements and the like so make are punishable by

fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code; and that such wilful false statements may jeopardise the validity of the application or any patent issuing thereon.

Signed: _____ Date: 8/3/99

Sean Duffy